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**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Paper No. 24

Application Number: 08/410,539
Filing Date: March 24, 1995
Appellant(s): Matthew B. Wheeler

Alice O. Martin
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed November 9, 1998.

(1) *Real Party in Interest*

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

This appeal involves claims 1-6, 9-12 and 15-20.

Claims 14 and 22-77 are withdrawn from consideration as not directed to the elected invention.

(4) *Status of Amendments After Final*

The amendment after final rejection filed on November 9, 1998 has been entered.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is substantially correct. Additional issues are as follows:

Claims 15-20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,523,226.

Claims 1-6, 9-12 and 15-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-16 and 48-50 of copending Application No. 08/473,030.

Appellant has indicated willingness to file terminal disclaimers (paper 21), so the double patenting rejections will not be discussed here.

(7) *Grouping of Claims*

Appellant's brief includes a statement that claims 1-6 and 9-12 do not stand or fall together with claims 15-20 and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) *Claims Appealed*

A substantially correct copy of the appealed claims appears on pages I-iii of the Appendix to the appellant's brief. The minor errors are as follows:

Claim 1 does not reflect the amendment filed September 16, 1997. Claim 1, at line 2, should read "...introducing a cultured ungulate embryonic stem cell..."

(9) *Prior Art of Record*

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

- | | | |
|-----------|---------|--------|
| 5,523,226 | WHEELER | 6-1996 |
|-----------|---------|--------|
- Wurst et al. "Production of targeted embryonic stem cell clones." In: Gene Targeting A Practical Approach, A.L. Joyner, ed., (1993), p. 33.
- Clark et al. "Germ line manipulation: applications in agriculture and biotechnology." In: Transgenic Animals, F. Grosveld et al., eds., (1992), p. 250.
- Kollias et al. "The study of gene regulation in transgenic mice." In: Transgenic Animals, F. Grosveld et al., eds., (1992), p. 92.

Nichols et al. "Establishment of germ-line-competent embryonic stem (ES) cells using differentiation inhibiting activity." *Development*, vol. 110 (1990), pp. 1341-1348.

Bazer et al. "Fertilization, Cleavage and Implantation." In: *Reproduction in Farm Animals*, E.S.E. Hafez, ed., (1987), pp. 210-228.

Piedrahita et al. "On the isolation of embryonic stem cells: Comparative behavior of murine, porcine and ovine embryos." *Theriogenology*, vol. 34, no. 5 (November 1990), pp. 879-901.

Cruz et al. "Origin of Embryonic and Extraembryonic Cell Lineages in Mammalian Embryos." In: *Current Communications in Cell & Molecular Biology 4. Animal Applications of Research in Mammalian Development*, R.A. Pedersen et al., eds., (1991), pp. 147-204.

(10) *Grounds of Rejection*

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1-6, 9-12 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for swine, does not reasonably provide enablement for all ungulates. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is well settled that more than one working example may be required to enable a broad genus, particularly in an unpredictable art (MPEP 2164.02). The specification

acknowledges the unpredictability of the art, pointing out that the established method for producing mouse embryonic stem cells can not be applied to other species (paragraph bridging pp. 4-5).

The specification does not provide any working examples or specific guidance regarding production of embryonic stem (ES) cells of species other than swine. The parent application disclosed methods limited to production of swine ES cells. In the instant application, the specification has been amended to allege that the methods which were shown to be effective for swine are also effective for other ungulate species. There is reason to doubt this assertion, given the unpredictable nature of the art. Mammalian species differ in their embryonic development. Differences among species are acknowledged by Appellant (specification, p. 5). Cruz et al. list some of the differences in early embryonic development among swine, oxen, horses, goats and sheep (e.g. Table 1). Bazer et al. also provide an overview of differences among ungulate species (entire document). Piedrahita et al. observed that porcine and ovine embryos responded differently to the same treatments. Conditions which allowed production of porcine ES-like cell lines did not allow development of ovine ES-like cell lines (e.g. Table 1). Piedrahita et al. state, "Ovine intact embryos and isolated ICM behaved differently than porcine embryos" (p. 888). Furthermore, those skilled in the art recognize that not all "ES-like" cells are "true" ES cells, i.e. totipotent cells capable of contributing to the germ line of chimeric animals. The specification acknowledges the need to "validate" ES cells (p. 10).

Appellant has argued that the claimed methods have been used to produce sheep ES cells, citing the Wheeler declaration (paper 16). This argument is not persuasive because the ES-like cells disclosed in the declaration do not meet an important art-accepted criterion of an ES cell, the ability to be incorporated into all cell types of an organism, particularly the germ line. For example, Nichols et al. state that "[e]mbryonic stem cells...retain the ability to participate in normal embryonic development and, following reintroduction to the blastocyst, they generate chimaeric animals that are mosaic in *all* their tissues. Mosaicism extends to the germ cell lineage and *ES cells can contribute fully functional gametes.*" (p. 1341, first paragraph, emphasis added). Appellant has demonstrated that the disclosed sheep ES-like cells have an appearance similar to swine ES cells, but not that they can be used to generate chimeric sheep and contribute fully functional gametes. Additional examples from the art are cited below. Kollias et al. state that "[a]fter reintroduction into blastocysts, [ES cells] can contribute to all the tissues of the mice derived from the reimplanted blastocysts, *including germ line cells*" (p. 92, emphasis added). Wurst et al. state that "ES cells resemble in many aspects ICM cells *especially in their ability to contribute to all tissues in chimeras*" (p. 33). Clark et al., discussing the isolation of putative swine ES cell lines, state that "[t]he isolation of ES cells from domestic livestock has not yet been conclusively demonstrated...[P]ig cells have been...used in blastocyst injection experiments. Preliminary results indicate...that these cells can contribute to tissues in the developing animal. *Demonstration that these cells are able to contribute to the germ line is awaited*" (p. 250, second full paragraph; emphasis added). Finally, Appellant himself has stated, "True totipotent embryonic cell types are those

capable of being induced to develop into any cell type present in an entire animal" (Wheeler, col. 2, lines 61-64). Hence those skilled in the art would not accept the ES-like cells described in the declaration as "true" ES cells based solely on their appearance, particularly since true sheep ES cells have not been produced previously and so there is no standard for comparison. In conclusion, there is no convincing evidence on the record that the disclosed methods will yield "true" ES cells of any species other than swine.

(N.B. The ability of the disclosed swine ES cells to contribute to the germ line was demonstrated in a declaration filed in the parent application, now patent no. 5,523,226.)

(11) Response to Argument

Appellant argues that the Examiner did not define what a "working example" is, nor indicate what other factors are considered when determining whether a specification is enabling. This is false. A working example was defined in the final rejection and, while it is hard to believe that any practitioner could not be aware of the "*Wands* factors," these are clearly set forth in the portion of the MPEP cited in the final rejection (paper 17, p. 3).

Appellant argues that the specification provides guidance regarding species other than swine. This may be true, but there is no evidence that the methods described in the specification produce ES cells of species other than swine. The art relied upon by the Examiner clearly establishes that those skilled in the art view reports of "ES cells" with skepticism, and that one skilled in the art would not recognize cells that "look like ES cells" (such as those described in the Wheeler declaration) as "true" ES cells until their competence to contribute to the germ line was demonstrated. There is good reason for this skepticism, as

shown by the numerous published PCT applications (submitted in Appellant's information disclosure statement) which erroneously claimed to have produced ES cells of various ungulate species.

Appellant argues that ungulates are more closely related to each other than to rodents. This argument is not persuasive for two reasons. First, an ungulate is any mammal with hooves. This includes not only swine, sheep and cattle, but also horses, elephants, camels, tapirs, hyraxes, rhinoceroses, giraffes, etc. The Ungulata encompasses many taxonomic genera having divergent anatomical and physiological characteristics. Even the less "exotic" ungulates are classified in different genera. For example, pigs are in the genus *Sus*, cattle in the genus *Bos*, sheep in the genus *Ovis*, horses in the genus *Equus*, etc. Second, even if all ungulates were closely related, this would not assure that the methods which work for swine would work for other species. The established methods for producing mouse ES cells have not been successfully applied to other rodent species such as rat, for example.

In conclusion, the claims are broad, encompassing many divergent taxonomic groups. The state of the prior art is that others had incorrectly asserted that they had done what Appellant now claims, resulting in the skilled artisan setting a high standard of proof (demonstration of germ line transmission) before accepting that a cell line is an "ES cell line." This standard has been met only for swine; there are no other working examples. The art is unpredictable. It appears that the quantity of experimentation required to make and use the claimed invention for species other than swine would be high.

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For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

BRC
February 3, 1999



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